THE PHYSIOLOGY OF GLYCOSURIA.*

By MARTIN H. FISCHER, M. D., Oakland.

The presence of dextrose in the urine is so greatly the predominating sign of a diabetes mellitus that a brief study of the physiology of glycosuria may well be regarded as a prerequisite to an intelligent understanding of the disease itself. While other forms of sugar besides dextrose are found in the urine in various conditions—for instance, sucrose after enjoyment of too large amounts of this sugar, or lactose in nursing mothers—the form of mellituria to which the following remarks refer is dextrosuria and the only sugar considered is dextrose.

Under what circumstances, first of all, do we find dextrose in the urine? So far as human beings, and at least the majority of animals examined in this regard are concerned, there can be no doubt that sugar is always present in traces in the urine of even entirely normal individuals. But this amount of sugar is too small to be recognized save by expert chemical means and has from the standpoint of the physiology of glycosuria more a theoretical than a practical interest.

By the term glycosuria, we may now recognize any increase in the amount of dextrose in the urine above this trifling normal amount. What are the causes that lead to such a glycosuria? While, as we shall see, these may be many and various, they can all be grouped under two classes, namely, such as lead to an increased permeability of the kidney cells to dextrose, and second, such as increase the concentration of this sugar in the circulating blood. Under all ordinary circumstances, the circulating blood contains dextrose, but the per cent. present, while subject to considerable variations, at no times normally exceeds (about) 0.2%. When the concentration of sugar in the blood exceeds this value, the kidney cells are unable to hold it back, and some of it goes over into the urine. The same end is accomplished when, instead of raising the per cent. of sugar in the blood, the permeability of the kidney cells is increased so that sugar may now go over into the urine even when present in less than 0.2% in the blood.

Let us now consider in somewhat greater detail the varied circumstances which may bring about one or the other of these two conditions.

(1). *The glycosurias not associated with an increase in the concentration of sugar in the blood.*

Under this heading fall the renal diabetes, of which, so far as I know, only three experimental forms exist. The first of these is the phloridzin or phloretin glycosuria. If either one of these substances—of which phloridzin represents the glucoside of the other—is introduced intravenously, subcutaneously or per os into an animal, an excretion of dextrose begins in the urine within a few hours after its administration and, continuing from one to several days, ceases when all of the poison has been eliminated. During the entire time of the glycosuria no increase in the concentration of sugar in the blood is noted.

Such an increase in the permeability of the kidneys to sugar is observed also after the intravenous injection of pure sodium chloride (and other salt) solutions. A third experimental form is that accompanying the increased urinary flow following the administration of caffeine, theobromine and diuretin.

From the standpoint of finding a counterpart in human glycosurias, the described forms are probably without interest. From theoretical considerations alone, there seems to exist no reason why a renal diabetes should not exist in human beings; but up to the present time there seems to be little evidence to sustain the belief that the described clinical cases are not such as have complicated rather than followed upon a kidney lesion.

(2). *The glycosurias associated with an increase in the concentration of sugar in the blood.*

Under this heading fall the majority of the experimental glycosurias, and probably all the clinical forms. It is well to begin our consideration of this group with a reference to the glycosuria which follows the ingestion of excessive amounts of carbohydrates. Generally speaking, every animal can be made to excrete sugar in the urine above the normal amount if only sufficient carbohydrate be consumed in a sufficiently short period of time. Under such circumstances a rapid absorption of sugar is liable to occur, with a resulting increase in the concentration of the blood going to the liver. As soon as this increase exceeds the point below which the liver is capable of converting this sugar into glycogen, and so storing it, the sugar passes on into the general circulation, and if present in this above 0.2 per cent is eliminated in the urine. When present in excessive amounts, a second road of absorption is open to the carbohydrates found in the alimentary tract, especially in the lower portions of the small intestine. Under such circumstances sugar passes into the lymph and then through the thoracic duct enters the general circulation, whereby the kidneys are finally reached.

It is clear that a number of factors play a role in bringing about such an "alimentary glycosuria," among which need only be mentioned the rate of feeding, the amount of feeding, the kind of carbohydrate fed, the rate of absorption, the region of absorption, the amount of sugar already in the blood, the condition of the liver, the condition of the muscles, and the state of the kidneys. After what has been said, it will not seem strange that the "toleration limit" for carbohydrates is different, not only in different individuals, but in the same individual under different circumstances. We see also how, through pathological states of the most varied kinds, what may be called the normal toleration limit of an individual can be markedly decreased, as illustrated in the infinite number of grades of glycosuria noted in diabetics.

With these remarks on a physiological glycosuria as determined through excessive consumption of

* Presented as one of the papers in a symposium on Diabetes, California State Medical meeting, Del Monte, 1907.

carbohydrates, we can pass to an experimental, pathological form of glycosuria, namely, that which follows puncture of the floor of the fourth ventricle. Shortly after such an injury the per cent of dextrose in the blood begins to rise, and usually within an hour sugar appears in the urine. This excretion of sugar may continue for several days, at the end of which time the liver is found (practically) free from glycogen and sugar. It seems most plausible to suppose that injury to the medulla serves as a stimulus to nerve fibers which pass by way of the splanchnics to the liver, for if the splanchnics are cut, the diabetic puncture is ineffective. How the splanchnics affect the liver so as to make the glycogen in this organ break down into dextrose, and so allow this to pass into the general circulation, thereby raising the concentration of sugar here, is not known.

Instead of directly injuring the medulla it is possible to affect this indirectly and so bring about a glycosuria. Two roads are open for thus indirectly affecting the medulla, namely, the nervous and the circulatory systems, and it will not seem strange in consequence to find grouped side by side with Claude Bernard's diabetic puncture the now to be discussed experimental glycosurias.

Stimulation of the central end of practically any of the afferent nerves is followed by glycosuria. As the more striking examples we need only mention the sciatic, the vagus and the trifacial. As all of these stand in intimate anatomical relation to the medulla, it is conceivable that impulses traveling up these nerves affect the nerve cells found in the medulla, and that from here impulses pass over the splanchnics to the liver. This conception finds experimental support in the fact that division of the splanchnics renders these methods of inducing glycosuria ineffective.

A number of substances which may be injected into the blood are capable of affecting the medulla and bringing about a glycosuria. The chloride, iodide, bromide and nitrate of sodium are all effective in this regard, as also the chlorides of lithium, potassium and strontium. Interesting is the fact that in a suitably arranged experiment calcium chloride is able to inhibit the action of any sodium salt in bringing about a glycosuria.

Into this same group with the salts I am inclined to put the acids (lactic, phosphoric, sulphuric, hydrochloric, etc.) which have been found capable of inducing a glycosuria. It is easily imaginable that a change similar in character to that produced in the medulla by salts (a change in the colloids?) might be as readily brought about through acids.

The glycosuria which follows lack of oxygen, or any condition which in its ultimate analysis leads to a lack of oxygen, such as poisoning by carbon monoxide, curare, strychnine or tetanus toxine, must also be considered under this heading, for we know that, as a result of lack of oxygen, various acids and other poisonous substances are produced in tissues which we have no reason to consider act differently from the acids or salts that are introduced indirectly into the circulation. From unpublished experiments, morphine no doubt also belongs in this class.

Various anæsthetics are also capable of producing a glycosuria, apparently through their action on the central nervous system. Chloroform and ether constitute striking examples. Chloral seems to affect not only the nervous system, but also the kidneys, in a way similar to that of phloretin.

The pancreatic form of glycosuria constitutes another type of the class associated with an increase in the concentration of sugar in the blood. If the pancreas is entirely removed from an animal, an excretion of sugar in the urine begins within a few hours. The glycosuria brought about by this means is the most intense of the experimental types and is associated with all the signs and symptoms of the severest diabetes. The excretion of sugar is not due to a lack of the pancreatic enzymes in the intestinal lumen, for simple ligature of the pancreatic ducts is not followed by glycosuria. Nor does glycosuria result if the entire gland is extirpated, but a piece of the pancreas is transplanted under the skin. But let this piece be removed, and sugar promptly appears in the urine. The facts are explained by saying that the pancreas gives off an internal secretion to the blood, the presence of which is necessary for a proper carbohydrate metabolism. The nature of this relation of an unknown constituent of the pancreas to carbohydrate metabolism is unknown. Experiments exist which claim to prove that, while extracts made from either muscle or pancreas are incapable of splitting dextrose, a mixture of these two does so readily. But these observations have been severely criticised.

With pancreatic glycosuria we have to consider the glycosuria which follows the intravenous injection of adrenalin. We know that this substance owes its effect to its action upon the pancreas. When locally applied to this organ a glycosuria soon results. With adrenalin can be classed a long series of chemicals which have nothing in common with adrenalin except a reducing action. The cyanides, when locally applied to the pancreas, also bring about a glycosuria, apaprently through an action which results indirectly in the production of reducing substances within the pancreas.

A last (as yet not well established) form of glycosuria, is the hepatic. The injection of ether and certain other substances into the portal vein is followed by the appearance of sugar in the urine. Clinically this hepatic form of glycosuria finds a parallel in the glycosurias associated with liver cirrhoses.

All the forms of glycosuria enumerated have been claimed to have their clinical parallels. Every one has heard of nervous and pancreatic forms of diabetes, of glycosurias associated with injuries to nerves, liver, etc.; but too many of these parallels have been hastily drawn and upon the slippery ground of clinical observation.

In the foregoing only such measures have been considered as experiment has actually proved effect-

ive in bringing about a glycosuria. It must be clear to every one, however, that these in no sense constitute *all* the possible disturbances which we may imagine capable of so interfering with the consumption, absorption, storage, utilization and elimination of the various carbohydrates (and other foodstuffs) as to lead to a glycosuria.*

Sugar may appear in the urine in consequence of any of a dozen causes and, it is well to remember, without any morphological evidence. The valuelessness of morphological pathology to give us an insight into the nature of many of the so-called metabolic diseases shows itself nowhere better than in this very subject of diabetes, to an understanding of which not one morphological pathologist has contributed. In the end the solution of the problem lies with the physiological chemist, more probably still with the physical chemist.

Attempts have been made at various times to reduce the cause of all glycosurias associated with an increase in the concentration of sugar in the blood to one fundamental change in carbohydrate metabolism, such as an interference with certain obscure nervous influences on the liver, a decreased power of the tissues to oxidize dextrose, etc. None of these have succeeded, and it would be strange if they did. In fact, most of the evidence is in favor of the idea that an increase in the per cent of sugar in the blood may be the expression of any one or more of a series of such fundamental changes. As the most striking experimental evidence in this direction we have the effect of puncture of the medulla upon an animal rendered diabetic through removal of the pancreas. Here the glycosuria, already intense through extirpation of the pancreas, becomes still more severe when the medulla is injured.

Nothing has been said regarding the evil consequences of a glycosuria. The mere loss of a certain amount of sugar by an organism, while not harmless, is comparatively unimportant. When the tissues are persistently bathed in a sugar solution having a concentration above the normal, they suffer a certain intoxication; but the experiments made to prove this are not very satisfactory. The chief effects of a glycosuria are therefore not at all those of the glycosuria itself, but are dependent upon the changes in metabolism which so frequently accompany a glycosuria. Scattered experiments show that in animals rendered glycosuric by various means, poisonous chemical substances — for example, organic acids of various kinds — are formed in large amounts. The action of these upon the organism then gives rise to the intoxications observed. In addition to the changes in carbohydrate metabolism, disturbances in nitrogenous metabolism frequently accompany glycosuria; but into a discussion of this question we can not enter.

I have been asked to give in my paper a definition of diabetes mellitus. It would be absurd to repeat that it is a disease the cardinal sign of which is a more or less persistent excretion of dextrose in the urine, for while some would include under this heading glycosurias which after persisting a number of days or weeks disappear under treatment, others consider no glycosuria a diabetes mellitus unless it persists in spite of all treatment and finally kills its victim. The simplest way out of such a difficulty is found in making a definition fit facts instead of facts a definition. Until such time as we can clinically say, glycosuria due to pressure of a tumor on the medulla or to lack of a certain constituent of the pancreas, why do we not hold to the facts at our disposal and say, persistent glycosuria of unknown cause, transitory glycosuria due to pressure of a gumma on the vagus, etc., and so forget entirely our diabetes mellitus which serves at present, particularly for those glycosurias the origin of which is obscure?

*Experimental observations are at hand, for example, which render it not impossible that the synthesis and analysis of glycogen in the liver represents a reversible process occurring under the influence of perhaps one, possibly two ferments. It is an easy matter to imagine how such a reaction, which under ordinary circumstances has a certain equilibrium point, can be influenced by a whole series of external conditions that displace this equilibrium point more or less toward one side or the other. In this way the ordinary relationship of sugar to glycogen might be so altered that equilibrium is established when less glycogen exists beside the sugar than under normal circumstances. This would allow the sugar in the blood to reach a higher concentration than normal, and when sufficiently great, to appear in the urine. Such reasoning should make us beware of any attempt which tries to explain all glycosurias on one basis.

CONCERNING THE NECESSITY OF WATCHING THE HEART IN DIABETES.*

By C. M. RICHTER, M. D., San Francisco.

It is my purpose in this paper to emphasize the importance of watching the heart of a diabetic.

For over 30 years I have considered it my duty to examine carefully into the condition of the heart whenever the patient presented any serious illness of any description. I make it my duty then to examine the heart carefully at every visit. It has been my privilege in consequence to become aware of many changes in the heart's action, as we find them recorded in the medical literature of the last five years, and to forestall to some degree that changes in the heart's action, in the sounds of the heart, in the size of the heart, etc., are exceedingly frequent during any serious illness. If you look at the textbooks on diabetes you will find for instance in the 1906 edition of Osler under Morbid Anatomy of Diabetes the two lines, "The heart is hypertrophied in some cases—endocarditis is very rare; arteriosclerosis is common." Naunyn in his second edition of 1906 (Nothnagel series) considers arterio-sclerosis complication as very common. He refers to disturbance of circulation in a great many patients, who suffer from *mild* diabetes and are above 40 years of age, principally blaming the arterio-sclerosis for such symptoms. But he considers it as possible, that the diabetes may entirely disappear during an aggravation of the symptoms made by arteriosclerosis. He speaks of the feebleness and debility of diabetics, when their nutrition suffers, but ignores the heart's condition in reference to it. However, he says, on page 261, "Schmitz machte

*Read at the Thirty-seventh annual meeting of the State Society, Del Monte, April, 1907.